lesion revascularization with XIENCE V stent such that at the end of one year, we actually see, just like we saw in SPIRIT II, a significant 43 percent reduction in major adverse cardiovascular events with one drug-eluting stent versus the other TAXUS stent. So 5.9 percent with XIENCE V, 10.2 percent with TAXUS. And this is a fairly striking 43 percent reduction.

So here are all the one-year result endpoint event rates. One can see again stent thrombosis, both per-protocol and by the ARC definitions, infrequent in both groups and no different; cardiac death, also infrequent in both groups and not different; overall myocardial infarctions out to one year, somewhat catch up.

And you can see 2.8 percent with XIENCE V, 4.1 percent with TAXUS. Target lesion revascularization in this trial, of course, very underpowered for this endpoint, tended to be numerically less with XIENCE V

compared to TAXUS, so overall major adverse cardiovascular events.

And this is now using binomial numbers, slightly different than what I showed you at the hazard curves. This is a relative risk but a 42 percent reduction confidence interval, .37 to .90, 10.3 percent with TAXUS reduced to 6 percent with XIENCE.

This trial, with more complex lesions and patients, actually had a significantly higher rate of the noise, if you will, additional revascularizations outside the target lesion but similar between the two stents, as one would expect. And, therefore, when one looks at TVF, it somewhat dilutes the ability to see differences compared to MACE. Nonetheless, you see this numerical trend, not statistically significant for a 24 percent reduction in TVF with XIENCE compared to TAXUS.

Thus, the conclusions from SPIRIT III was that the pivotal United States-based

SPIRIT III trial met both its pre-specified primary and major secondary or co-primary endpoints, demonstrating superiority of the XIENCE V stent compared to the TAXUS stent in reducing angiographic in-segment late loss and non-inferiority with regard to the nine-month endpoint of target vessel failure.

Now what I am going to do is present to you data from a true patient-level pooled meta-analysis of the SPIRIT II and III trials. So what is the rationale for doing this? With the time that the SPIRIT III trial was designed, the regulatory burden that was agreed upon with the FDA for approval of the XIENCE V stent was the demonstration of non-inferiority for angiographic late loss and target vessel failure compared to TAXUS. That required randomization of 1,002 patients.

But since that time, interest has shifted to examination of lower frequency safety and efficacy endpoints, such as death, myocardial infarction, stent thrombosis, and

target lesion revascularization. Neither SPIRIT II nor SPIRIT III was powered to examine the rates of these endpoints.

Thus, at the request of FDA, to provide more power to examine infrequent events, we have combined SPIRIT II and SPIRIT III in a true patient-level pooled meta-analysis. And this is very valid to do compared to some other meta-analyses because in SPIRIT II and SPIRIT III, patients with similar inclusion and exclusion criteria were randomized in two consecutive randomized trials, XIENCE V versus TAXUS. And follow-up has now been completed to one year in both trials.

So this summarized is the patients enrolled in the study, again similar inclusion and exclusion criteria, up to two de novo lesions with a maximum of one lesion per epicardial vessel. The reference vessel diameter was 2.5 to 3.75. And the lesion lengths were up to 28 millimeters.

There were 3 patients of the 1,302 that I described in SPIRIT II that did receive 4-millimeter stents, but that is really the only difference between these 2 randomized trials.

So 1,302 patients, 1,506 lesions. We have more power to look at low-frequency safety events and efficacy events, 892 randomized to XIENCE V, 410 randomized to TAXUS. These were two consecutive prospective single-blind trials with similar inclusion and exclusion criteria.

Now, importantly, we actually asked Abbott that we at the Cardiovascular Research Foundation, which is affiliated with Columbia University Medical Center, that we wanted to perform this analysis unhindered, if you will, by industry. So we asked them to provide both complete databases from the SPIRIT II and SPIRIT III trial for this unrestricted academic analysis. And we pre-specified the endpoints.

This is very similar to what we did for all the CYPHER and TAXUS trials that were published approximately six months ago in the New England Journal. We pre-specified superiority testing on all endpoints, but also all of these analyses should be considered exploratory and hypothesis-generating.

These are the baseline characteristics of the 892 XIENCE V patients and the 410 TAXUS patients. And they're very reflective of what we saw in both trials individually. In general, they were well-matched between the two groups.

The mean age, as you can see, was about 63 years. Approximately 30 percent of the 1,300 patients were women. And a relatively high proportion, about 28 percent, had diabetes mellitus, otherwise relatively similar to what we have seen in most of the versus DES trials.

With the one unique feature that all of the previous trials with TAXUS and

CYPHER only allowed a single lesion and a single vessel, we had 16 percent of the patients that had 2 lesions and 2 vessels randomized to either XIENCE versus TAXUS.

When one looks at the vessels that were enrolled in these patients, they were distributed throughout the coronary tree with about 42 percent of them being in the left anterior descending artery. And when one looks at quantitative coronary angiography, it was very closely matched in the 2 groups, about 2.76 millimeters, so relatively small vessels, and lesion lengths about 14.4 millimeters, so moderately long lesions. And this is 1,506 total lesions.

Now, first if you look at the 30-day outcomes -- and this is where we first start to really see differences that may become clinically important -- at 30 days, there were no cases of cardiac death in either SPIRIT II or SPIRIT III, but there was a statistically significant reduction in

myocardial infarctions from 2.9 percent with the TAXUS stent versus one percent with the XIENCE V stent, a 66 percent reduction. Thus, the composite endpoint of cardiac death or MI, of course, had the exact same numbers since there were no cardiac deaths.

Now, we don't expect many TLRs at 30 days with any sort of stent, and there weren't many, similar with the 2 stents. Thus, both major adverse cardiovascular events and target vessel failure were actually improved at 30 days with the XIENCE V stent compared to the TAXUS stent.

Now, we don't know in detail why this was, but, actually, this is not surprising. I was actually the first one to point out that in TAXUS V, we do have a higher rate of peri-procedural myocardial infarctions with the larger strut stent that we had tested in that study. And presumably it's the thinner stet strut and the more adhesive polymer that has less bonding, webbing, et

cetera, that is potentially less thrombogenic that leads to less side-branch compromise and perhaps other events that leads to an enhanced safety profile at 30 days.

Now, these are not only small, tiny myocardial infarctions. When we look at the level of the myocardial infarction as estimated by the peak CPK less than five, which we could consider small MIs, versus five to ten, which you might consider moderate sized MIs, versus greater than ten times the upper limits of normal, which are large MIs and nobody would argue are prognostically important, you can see that the XIENCE V stent compared to the TAXUS stent tends to reduce the levels of all sorts of MI, small, moderate, and large.

Now if we go to the one-year outcomes in these trials, first, I will show you the lower-frequency safety events. This is stent thrombosis with a pre-specified protocol definition. And one can see almost

identical rates of stent thrombosis out to one year with these two devices: 0.8 percent with TAXUS, 0.7 percent with XIENCE.

When we used the ARC definite or probable definitions, again, this is what most people are using right now, you can see that, again, out at one year, there is no difference in stent thrombosis between the 2 devices: 0.8 percent with TAXUS and with XIENCE V.

If we look at all-cause death at one year, all-cause death is infrequent. And there is no difference in all-cause death, 1.8 percent with TAXUS and 1.3 percent with XIENCE. What you are going to see in all of the next series of slides is that while these low-frequency safety events tend not to be different, you will see that they do tend to benefit or favor the XIENCE V stent, at least in terms of lower numerical rates of adverse events, which is reassuring.

So if we look at cardiac death at one year, one percent with TAXUS, zero percent

with XIENCE V, of course, low frequency, still not statistically significant but reassuring, when we look at MIs, I showed you that the 30-day MI rates were statistically significant.

And the curves stay roughly parallel since that time, so overall MIs out to one year, 4 percent with TAXUS, 2.3 percent with XIENCE, a relative 44 percent reduction with a borderline p-value of 0.08.

Thus, looking at our pre-specified endpoint of cardiac death or myocardial infarction at one year, again, you can see that it tends to favor the XIENCE V stent, 2.7 percent versus 4.5 percent with TAXUS, a relative 40 percent reduction, but the p-value is .10.

Now, if we look at efficacy measures, this is where it starts to also become revealing because we actually do see a statistically significant reduction in target lesion revascularization or clinical

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Fact Sheet

XIENCE V® Drug Eluting Stent

Key Facts

- The XIENCE V Everolimus Eluting Coronary Stent System is the only drug eluting stent (DES) to demonstrate superiority versus Taxus in two randomized, head-to-head, pivotal (phase III) clinical trials
- XIENCE V is an important next-generation treatment option combining impressive deliverability with demonstrated efficacy and safety
- The proven design of the MULTI-LINK VISION® Coronary Stent System, which XIENCE V is built upon, allows for ease of stent delivery to the blocked portion of the artery

Xience V®
Everolimus Eluting
Coronary Stent System

Overview

The XIENCE V® Everolimus Eluting Coronary Stent System was approved in the United States in July 2008 and internationally in October 2006. This next-generation drug eluting stent (DES) is used to treat coronary artery disease (CAD) by propping open a narrowed or blocked artery and releasing the drug, everolimus, in a controlled manner to prevent the artery from renarrowing following a stent procedure. XIENCE V is the only DES to demonstrate superiority versus Taxus® in two randomized, head-to-head, pivotal (phase III) clinical trials. In the SPIRIT II trial of 300 patients, XIENCE V demonstrated superiority to the TAXUS® paclitaxel-eluting coronary stent systems in the trial's primary endpoint of in-stent late loss, with a statistically significant 69 percent reduction at six months (0.11mm vs 0.36mm). Both TAXUS® Express²™ (73% of lesions) and TAXUS® Liberte® (27% of lesions) were used as controls in the SPIRIT II trial. In the SPIRIT III trial of 1,002 patients, XIENCE V demonstrated superiority to TAXUS Express² in the trial's primary endpoint of in-segment late loss (a measure of vessel renarrowing after a stent procedure), with a statistically significant 50 percent reduction at eight months (0.14mm vs 0.28mm).

Proven Design

XIENCE V is built upon the proven MULTI-LINK VISION® Coronary Stent System, which facilitates ease of delivery with a flexible design. Each element – the drug that is used, the concentration of the drug, the rate of elution, the composition of the polymer

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coating, the stent platform and the delivery system – is important in overall clinical safety and efficacy outcomes.

- XIENCE V is easily delivered to the narrowed or blocked artery, as it has the thinnest DES platform available
- The proven polymer coating on XIENCE V facilitates the release of the drug everolimus, getting it to the right place at the right time
- Everolimus has been shown to reduce tissue growth and inflammation – two factors tied to restenosis, or the renarrowing of an artery following a stent procedure

Additional Clinical Data

Data from the SPIRIT trials continue to demonstrate efficacy and safety for patients. Two-year data from the pivotal SPIRIT III clinical trial, which compares XIENCE V to TAXUS Express^2, include:

- A 45 percent reduction in the risk of major adverse cardiac events (MACE – an important clinical measure of safety and efficacy outcomes for patients including cardiac death, heart attack and the need for retreatment) at two years compared to TAXUS Express^2 (7.3% for XIENCE V vs. 12.8% for TAXUS Express^2).
- A 32 percent reduction in the risk of target vessel failure (TVF – a composite measure of safety and efficacy outcomes related to the treated vessel including cardiac death, heart attack and target vessel revascularization) compared to TAXUS Express^2 (10.7% for XIENCE V vs. 15.4% for TAXUS Express^2).

The SPIRIT Family of Trials

Abbott is committed to the long term, careful follow-up of patients in XIENCE V studies for years to come. The SPIRIT Clinical Trial Program includes eight different trials to evaluate XIENCE V for the treatment of CAD. These studies include:

- SPIRIT FIRST – A first-in-man study comparing XIENCE V with the MULTI-LINK VISION metallic stent system in 60 patients
- SPIRIT II – A 300 patient randomized, single-blind prospective clinical trial evaluating XIENCE V versus TAXUS (Express^2 and Liberte) in Europe and Asia Pacific
- SPIRIT III – A large-scale pivotal clinical trial comparing XIENCE V to TAXUS Express^2 in 1,002 patients in the United States
- SPIRIT IV – A 3,690 patient continued access trial to evaluate the safety and efficacy of XIENCE V for the treatment of CAD in a more complex patient population in the United States
- SPIRIT V – An international clinical trial that provides additional clinical experience with XIENCE V in approximately 3,000 patients at approximately

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100 clinical sites in Europe, Asia, Canada (including 7 Canadian sites) and Latin America

- XIENCE V SPIRIT WOMEN – The world's first DES trial to study only women, will evaluate 2,000 women receiving stents and the performance of XIENCE V in those patients in Europe, Asia-Pacific, Canada and Latin America
- XIENCE V USA: As part of its commitment to advancing the treatment of vascular disease, this post-market registry will evaluate outcomes in at least 5,000 patients with follow-up out to five years.
- XIENCE V INDIA: Similar to XIENCE V USA, this post-market registry will evaluate clinical outcomes in approximately 1,000 patients in India with follow-up out to five years.

Across its entire continued access and post-approval program, Abbott projects enrolling more than 14,000 XIENCE V patients.

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The XIENCE™ V Everolimus Eluting Coronary Stent System
Instructions for Use

℞ ONLY

Table of Contents

1.0 PRODUCT DESCRIPTION

The XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE V EECSS or XIENCE V stent system) is a device/drug combination product consisting of either the MULTI-LINK VISION® Coronary Stent System or the MULTI-LINK MINI VISION® Coronary Stent System coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer.

1.1 Device Component Description

The device component consists of the MULTI-LINK MINI VISION or MULTI-LINK VISION stent mounted onto the MULTI-LINK MINI VISION or MULTI-LINK VISION stent delivery system (SDS) respectively. The device component characteristics are summarized in Table 1-1.

Table 1-1: XIENCE V Stent System Product Description

	XIENCE V Rapid-Exchange (RX) EECSS	XIENCE V Over-the-Wire (OTW) EECSS
Available Stent Lengths (mm)	8, 12, 15, 18, 23, 28	8, 12, 15, 18, 23, 28
Available Stent Diameters (mm)	2.5, 2.75, 3.0, 3.5, 4.0	2.5, 2.75, 3.0, 3.5, 4.0
Stent Material	A medical grade L-605 cobalt chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent	
Drug Component	A conformal coating of a non-erodible polymer loaded with 100 µg/cm^2 of everolimus with a maximum nominal drug content of 181 µg on the large stent (4.0 x 28 mm)	
Delivery System Working Length	143 cm	143 cm
Delivery System Design	Single access port to inflation lumen. Guide wire exit notch is located 30 cm from tip. Designed for guide wires ≤ 0.014".	Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen. Designed for guide wires ≤ 0.014".
Stent Delivery System Balloon	A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length.	
Balloon Inflation Pressure	Nominal inflation pressure: 8 atm (811 kPa) for 2.5 and 2.75 mm diameters; 9 atm (912 kPa) for 3.0, 3.5, and 4.0 mm diameters Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes	
Guiding Catheter Inner Diameter	≥ 5 F (0.056")	
Catheter Shaft Outer Diameter (nominal)	2.5–3.0 mm / 3.5–4.0 mm Distal: 0.032" / 0.035" Proximal: 0.026" / 0.026"	2.5 mm / 2.75 x 8 – 3.5 x 18 / 3.5 x 23 – 4.0 x 28 Distal: 0.032" / 0.034" / 0.036" Proximal: 0.042" / 0.042" / 0.042"

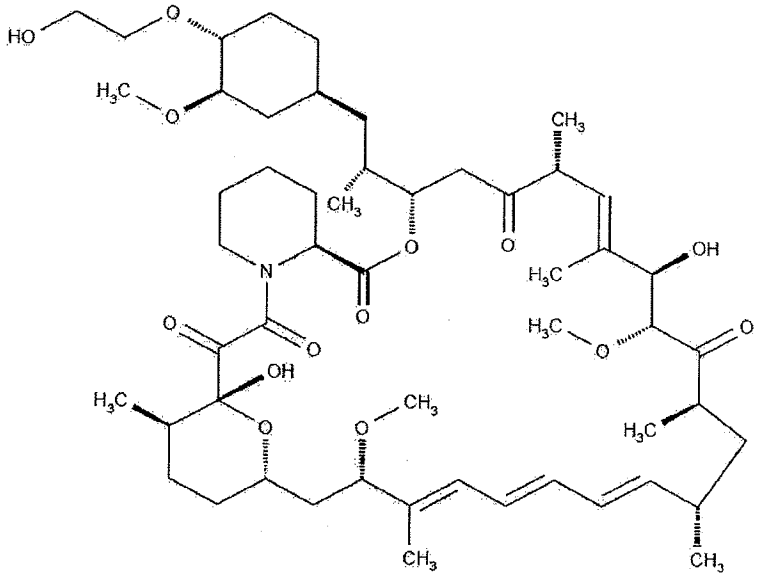
1.2 Drug Component Description

The XIENCE V Everolimus Eluting Coronary Stent (XIENCE V stent) is coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

1.2.1 Everolimus

Everolimus is the active pharmaceutical ingredient in the XIENCE V stent. It is a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin (sirolimus). The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in Figure 1-1 below.

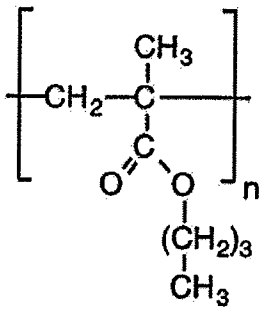
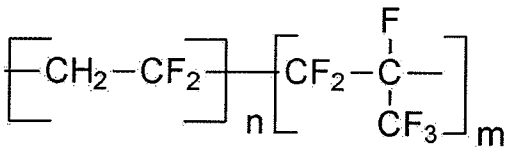
Figure 1-1: Everolimus Chemical Structure



1.2.2. Inactive Ingredients – Non-erodible Polymer

The XIENCE V stent contains inactive ingredients including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA coated stent surface. The drug load is 100 $\mu g/cm^2$ for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in Figure 1-2 below.

Figure 1-2: Non-erodible Polymer Chemical Structures

PBMA	PVDF-HFP
	

1.2.3 Product Matrix and Everolimus Content

Table 1-3: XIENCE V EECSS Product Matrix and Everolimus Content

Model Number (RX)	Model Number (OTW)	Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
1009539-08	1009545-08	2.5	8	37
1009540-08	1009546-08	2.75	8	37
1009541-08	1009547-08	3.0	8	37
1009542-08	1009548-08	3.5	8	53
1009543-08	1009549-08	4.0	8	53
1009539-12	1009545-12	2.5	12	56
1009540-12	1009546-12	2.75	12	56
1009541-12	1009547-12	3.0	12	56
1009542-12	1009548-12	3.5	12	75
1009543-12	1009549-12	4.0	12	75
1009539-15	1009545-15	2.5	15	75
1009540-15	1009546-15	2.75	15	75
1009541-15	1009547-15	3.0	15	75
1009542-15	1009548-15	3.5	15	98
1009543-15	1009549-15	4.0	15	98
1009539-18	1009545-18	2.5	18	88
1009540-18	1009546-18	2.75	18	88
1009541-18	1009547-18	3.0	18	88
1009542-18	1009548-18	3.5	18	113
1009543-18	1009549-18	4.0	18	113
1009539-23	1009545-23	2.5	23	113
1009540-23	1009546-23	2.75	23	113
1009541-23	1009547-23	3.0	23	113
1009542-23	1009548-23	3.5	23	151
1009543-23	1009549-23	4.0	23	151
1009539-28	1009545-28	2.5	28	132
1009540-28	1009546-28	2.75	28	132
1009541-28	1009547-28	3.0	28	132
1009542-28	1009548-28	3.5	28	181
1009543-28	1009549-28	4.0	28	181

2.0 INDICATIONS

The XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V stent) is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

3.0 CONTRAINDICATIONS

The XIENCE V stent is contraindicated for use in patients:

- Who cannot receive antiplatelet and/or anti-coagulant therapy (see **Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen** for more information)
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers

4.0 WARNINGS

- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Judicious patient selection is necessary because device use has been associated with stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy (see Section 5.2 for important information regarding antiplatelet therapy).

5.0 PRECAUTIONS

5.1 General Precautions

- Stent implantation should only be performed by physicians who have received appropriate training.
- Stent placement should be performed at hospitals where emergency coronary artery bypass graft surgery is accessible.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent is presently unknown.
- Risks and benefits should be considered in patients with severe contrast agent allergies.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from the XIENCE V SPIRIT family of trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic

Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (see Section 8.2 Stent Thrombosis Definitions and Section 9.4 SPIRIT II and SPIRIT III Pooled Analysis, for more information). In the XIENCE V SPIRIT family of trials analyzed to date, the differences in the incidence of stent thrombosis observed with the XIENCE V stent compared to the TAXUS stent have not been associated with an increased risk of cardiac death, MI, or all-cause mortality. Additional data from longer-term follow-up in the XIENCE V SPIRIT family of trials and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.

- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the XIENCE V SPIRIT family of trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.
- Orally administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglycerides levels.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In XIENCE V SPIRIT FIRST clinical trial, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 3 months post-procedure (75 mg per day). In XIENCE V SPIRIT II and SPIRIT III clinical trials, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 6 months post-procedure (75 mg per day). Aspirin was administered (a minimum of 75 mg per day) pre-procedure and continued for 1 to 5 years (depending on the study). Based on the case report forms from the SPIRIT II and III randomized clinical trials, approximately 92% of patients remained on dual antiplatelet therapy at 6 months and 62% at 1 year See Section 9.0 – Clinical Studies, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies on sirolimus-eluting or paclitaxel-eluting stents suggest that a longer duration of clopidogrel than was recommended post-procedurally in DES pivotal trials may be beneficial. Current guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines[1,2]).
- It is very important that the patient is compliant with the post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, MI, or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy. Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should

[1] Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121

[2] King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209

be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

5.3 Multiple Stent Use

A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. In the SPIRIT II and III clinical trials, treatment was limited to 36 mm of total stent length in up to two lesions in different epicardial vessels. Use of more than two stents to treat lesions longer than 28 mm has not been evaluated and may increase patient complication risks. Studies evaluating the effects of higher drug doses have not been conducted.

Effects of multiple stenting using XIENCE V stents combined with other drug-eluting stents are also unknown. When multiple drug-eluting stents are required, use only XIENCE V stents in order to avoid potential interactions with other drug-eluting or coated stents.

In addition, only stents composed of similar materials should be implanted in consecutive stent to stent contact to avoid corrosion potential between unrelated materials. Although *in vitro* tests combining L-605 CoCr alloy with 316 L stainless steel did not increase corrosion potential, these studies have not been conducted *in vivo*.

5.4 Brachytherapy

XIENCE V stent safety and effectiveness has not been evaluated in patients with prior target lesion or in-stent restenosis-related brachytherapy.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with XIENCE V stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

Pregnancy Category C. See Section 6.5 – Drug Information, Pregnancy. The XIENCE V stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a XIENCE V stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

5.6.2 Lactation

See Section 6.6 – Drug Information, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation considering the importance of the stent to the mother.

5.6.3 Gender

No safety- or effectiveness-related gender differences were observed in the individual XIENCE V clinical trials.

5.6.4 Ethnicity

Insufficient subject numbers prevent ethnicity-related analyses on XIENCE V safety and effectiveness.

5.6.5 Pediatric Use

Safety and effectiveness of the XIENCE V stent in pediatric subjects have not been established.

5.6.6 Geriatric Use

Clinical studies of the XIENCE V stent did not suggest that patients age 65 years and over differed with regard to safety and effectiveness compared to younger patients.

5.7 Lesion/Vessel Characteristics

Safety and effectiveness of the XIENCE V stent have not been established for subject populations with the following clinical settings:

- Unresolved vessel thrombus at the lesion site
- Coronary artery reference vessel diameters < 2.5 mm or > 4.25 mm
- Lesion lengths > 28 mm
- Lesions located in saphenous vein grafts
- Lesions located in unprotected left main coronary artery, ostial lesions, chronic total occlusions, lesions located at a bifurcation
- Previously stented lesions
- Diffuse disease or poor flow (TIMI < 1) distal to the identified lesions
- Excessive tortuosity proximal to or within the lesion
- Recent acute myocardial infarction (AMI) or evidence of thrombus in the target vessel
- Moderate or severe lesion calcification
- Multivessel disease
- In-stent restenosis
- Patients with longer than 24 months follow-up.

5.8 Drug Interactions

See Section 6.3 – Drug Information, Interactions with Drugs or Other Substances.
Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein. Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics).

Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a XIENCE V Stent.

5.9 Immune Suppression Potential

Everolimus, the XIENCE V stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the XIENCE V clinical trials. However, for patients who receive several XIENCE V stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

5.10 Lipid Elevation Potential

Oral everolimus use in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the XIENCE V stent are expected to be significantly lower than concentrations usually obtained in transplant patients. Increased serum cholesterol and triglycerides were not observed in the XIENCE V SPIRIT family of clinical trials.

5.11 Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated that the XIENCE V stent, in single and in overlapped configurations up to 68 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 720 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning or less

The XIENCE V stent should not migrate in this MRI environment. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the XIENCE V stent.

Stent heating was derived by relating the measured non-clinical, *in vitro* temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil to the local specific absorption rates (SARs) in a digitized human heart model. The maximum whole body averaged SAR was determined by validated calculation. At overlapped lengths up to 68 mm, the XIENCE V stent produced a non-clinical maximum local temperature rise of 3°C at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stents greater than 68 mm in length or stents with fractured struts are unknown.

As demonstrated in non-clinical testing, an image artifact can be present when scanning the XIENCE V stent. MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the XIENCE V stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of XIENCE V stents.

5.12 Stent Handling

- **Each stent is for single use only.** Do not resterilize or reuse this device. Note the "use by" (expiration) date on the product label.
- **The foil pouch is not a sterile barrier.** The inner header bag (pouch) within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.**
- **Do not remove the stent from the delivery system.** Removal may damage the stent and/or lead to stent embolization. These components are intended to perform together as a system.
- The delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or disrupt the stent on the balloon especially during delivery system removal from packaging, placement over the guide wire and advancement through the rotating hemostatic valve adapter and guiding catheter hub.
- **Do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.
- Use only the appropriate balloon inflation media (see Section 13.3.3 – Operator's Instructions, Delivery System Preparation). Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in stent deployment.

5.13 Stent Placement

5.13.1 Stent Preparation

- **Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed.** Use the balloon purging technique described in Section 13.3.3 – Operator's Instructions, Delivery System Preparation.
- **Do not induce negative pressure on the delivery system prior to placing the stent across the lesion.** This may cause dislodgement of the stent from the balloon.
- Use guiding catheters which have lumen sizes that are suitable to accommodate the stent delivery system (see Section 1.1 – Product Description, Device Component Description).

5.13.2 Stent Implantation

- The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the difficulty of stent placement and cause procedural complications.
- Do not expand the stent if it is not properly positioned in the vessel (see Section 5.14 – Precautions, Stent System Removal).
- Implanting a stent may lead to vessel dissection and acute closure requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- Although the safety and effectiveness of treating more than one vessel per coronary artery with XIENCE V stents has not been established, if this is performed, place the

stent in the distal lesion before the proximal lesion in order to minimize dislodgement risk incurred by traversing through deployed stents.

- Stent placement may compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** See Table 14-1, Typical XIENCE V EECSS Compliance. Balloon pressures should be monitored during inflation. Applying pressures higher than specified on the product label may result in a ruptured balloon with possible arterial damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- An unexpanded stent may be retracted into the guiding catheter one time only. An unexpanded stent should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter should not be performed as the stent may be damaged when retracting the undeployed stent back into the guiding catheter.
- Should **any resistance** be felt **at any time** during coronary stent system withdrawal, the stent delivery system and guiding catheter should be **removed as a single unit** (see Section 5.14 – Precautions, Stent System Removal).
- Stent retrieval methods (i.e., using additional wires, snares, and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Although the stent delivery system balloon is strong enough to expand the stent without rupture, a circumferential balloon tear distal to the stent and prior to complete stent expansion, could cause the balloon to become tethered to the stent, requiring surgical removal. In case of balloon rupture, it should be withdrawn and, if necessary, a new dilatation catheter exchanged over the guide wire to complete the expansion of the stent.
- Ensure the stented area covers the entire lesion/dissection site and that no gaps exist between stents.

5.14 Stent System Removal

Should **any resistance** be felt **at any time** during either lesion access or removing the delivery system post-stent implantation, the stent delivery system and the guiding catheter should be **removed as a single unit.**

When removing the delivery system and guiding catheter as a single unit, the following steps should be executed under direct visualization using fluoroscopy:

- Confirm complete balloon deflation. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position. In some cases it may be necessary to slightly retract the guiding catheter in order to prevent unplanned guiding catheter movement and subsequent vessel damage. In cases where unplanned guiding catheter movement has occurred, a coronary tree angiographic assessment should be undertaken to ensure that there is no damage to the coronary vasculature.
- DO NOT retract the delivery system into the guiding catheter.
- Position the proximal balloon marker just distal to guiding catheter tip.
- Advance the guide wire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter, and remove the guiding catheter and delivery system as a **single unit**.

Failure to follow these steps and/or applying excessive force to the delivery system can potentially result in loss or damage to the stent and/or delivery system components.

If it is necessary to retain guide wire position for subsequent artery/lesion access, leave the guide wire in place and remove all other system components.

Stent retrieval methods (i.e., additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include, but are not limited to, bleeding, hematoma, or pseudoaneurysm.

5.15 Post-Procedure

- When **crossing a newly deployed stent** with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter or delivery system, exercise care to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Antiplatelet therapy should be administered post-procedure (see Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen and Section 9.0 Clinical Studies). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.
- If the patient requires imaging, see Section 5.11 – Precautions, Magnetic Resonance Imaging (MRI).

6.0 DRUG INFORMATION

6.1 Mechanism of Action

The mechanism by which the XIENCE V Stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 stage.

6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent

Everolimus pharmacokinetics (PK) when eluted from the XIENCE V Stent post-implantation has been evaluated in three different substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the US randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The third PK substudy was conducted as part of the SPIRIT II clinical trial at sites in Europe, India, and New Zealand. Whole blood everolimus PK parameters determined from subjects receiving the XIENCE V stent are provided in Table 6-1.

Table 6-1: Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation

	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t}[a] (ng.h mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
SPIRIT III RCT and 4.0 Arm							
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=3[b])	88 µg	0.050 (0.50-1.88)	0.3867 ± 0.09866		5.31 ± 4.114		
3.5-4.0 x 28 mm (n=6[c])	181 µg	0.50 (0.07-1.00)	1.175 ± 0.6817	79.08 ± 57.24	23.73 ± 13.63	44.00 ± 28.67	5.130 ± 2.114
SPIRIT III Japanese Arm							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=6)	88 µg	1.00 (0.50-1.02)	0.5017 ± 0.1398	45.22 ± 35.08	5.049 ± 2.138	12.98 ± 7.078	9.286 ± 6.069
3.5-4.0 x 18 mm (n=4[b])	113 µg	0.51 (0.50-0.53)	0.6500 ± 0.08756	53.57 ± 19.34	11.02 ± 4.002	19.97 ± 7.890	6.471 ± 2.807
SPIRIT II Clinical Trial							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{last} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=13)	88 µg	0.50 (0.13-2.17)	0.4369 ± 0.1507	54.08 ± 35.78	8.255 ± 5.863	19.60 ± 15.30	8.066 ± 6.443
3.5-4.0 x 18 mm (n=4[c])	113 µg	0.50 (0.50-0.50)	0.5850 ± 0.2630	47.60 ± 62.13	42.54 ± 58.83	22.79 ± 31.47	16.96 ± 13.07
3.5-4.0 x 28 mm (n=4)	181 µg	0.46 (0.17-1.00)	0.7925 ± 0.1406	103.4 ± 64.17	28.07 ± 13.18	52.71 ± 27.40	5.332 ± 5.048

[a] Accurate determination not possible due to rapid disappearance of everolimus from the blood
[b] n= 5 for $t_{1/2}$ and CL
[c] n= 3 for $t_{1/2}$ and CL
t_{max}(h)= time to maximum concentration
C_{max}= maximum observed blood concentration
$t_{1/2}$ (h)= terminal phase half-life
AUC_{0-t} or AUC_{last} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
$AUC_{(0-\infty)}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL= total blood clearance

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, 1 subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all 3 studies, the C_{max} value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination; $t_{½}$, AUC_{0-t}, AUC_{last}, AUC_{∞}, and CL could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

Everolimus disappearance from circulation following XIENCE V stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies.

6.3 Interactions with Drugs or Other Substances

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods[3] listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavor, erythromycin, clarithromycin, fluconazole, calcium channel blockers)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepin, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit juice

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of XIENCE V stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group (XIENCE V stent). The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. Based on the results of this study, the XIENCE V stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies were conducted on the XIENCE V stent in mammalian cells and bacteria. These studies included gene mutations in bacteria (Ames Test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. Based on the results of these studies, the XIENCE V stent is not genotoxic.

[3] Certican® Investigator's Brochure. Novartis Pharmaceutical Corporation